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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,123	01/09/2002	Se-Chang Kwon	DE1325	6189

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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
12/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/031,123	KWON ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *11-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,18,19,21-24,26 and 27* is/are rejected.

7)☒ Claim(s) *17,20 and 25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 18 October 2007 has been entered.

Status of Application, Amendments, And/Or Claims

The after final amendment of 14 September 2007 has been entered as indicated in the advisory action of 21 September 2007 and requested in the RCE of 18 October 2007. Claims 1-27 are pending. Of these, claims 11-16 remain withdrawn from consideration as being directed to a non-elected invention. Claims 1-10 and 17-27 are under examination.

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 18, 19, 21-24, 26, and 27 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kuga et al. (US 5362853; issued 08 November 1994) in view of EP 0256843 A1 (published 1988) for reasons of record. For Applicant's convenience, the rejection is repeated here.

Kuga et al. teach a modified hG-CSF wherein amino acid 17 is replaced with Ser. See columns 27-28, especially the sentence bridging columns 27-28. This is relevant to claims 1-4. Kuga et al. also teach DNA and an expression vector encoding the modified G-CSF at the same place. This is relevant to claims 5-8, 22-24, 27. Note that the pCF plasmid vector base is an expression vector. See column 9, lines 9-15. Kuga et al. teach a transformed microorganism host cell, specifically *E, coli*, that comprises these DNA molecules. Col. 9, li. 9-15. This is relevant to claims 18, 19, 26. Finally, Kuga et al. teach a process for producing the modified G-CSF recombinantly using these products. *Ibid.* This is relevant to claim 21.

The *E. coli*-produced hG-CSF of Kuga also was not glycosylated (i.e., contained no sugar chain) as an inherent property of that molecule, since production of mammalian proteins in *E. coli* results in a non-glycosylated product. This is relevant to claims 1-8, 18, 19, 21-24, 26, and 27.

Kuga et al. do not specifically teach a modified hG-CSF lacking an N-terminal methionine. However, Kuga et al. do acknowledge that the addition of the N-terminal methionine is disadvantageous, and disclose enzymatic methods of removing the N-terminal methionine along with a few other N-terminal amino acids. See col. 46, li. 29-40.

EP 0256843A1 also teaches the advantage of G-CSF lacking the N-terminal methionine, and discloses how to achieve the same. See pp. 12-13 and claim 6.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Kuga et al. regarding substitution of unglycosylated hG-CSF so that residue 17 is Ser, by removing the N-terminal methionine residue as disclosed by EP 0256843A1 and suggested by Kuga et al., with a reasonable expectation of success. The motivation to do so can be found in both Kuga et al. and EP 0256842A1, which both discuss the disadvantage of having an N-terminal methionine.

Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

In the after final amendment of 14 September 2007, Applicant argues that Kuga does not teach how to make a modified hG-CSF lacking an N-terminal methionine and

instead suggests use of enzymatic cleavage. This has been fully considered but is not found to be persuasive for the following reasons. While it is true that Kuga's hG-CSF has an N-terminal methionine, Kuga also acknowledges how the N-terminal methionine is disadvantageous at col. 46, li. 29-40. EP 0256843A1 specifically teach how to use the enzymatic cleavage approach suggested by Kuga to make an hG-CSF that lacks the N-terminal methionine at pp. 12-13 and claim 6. Therefore, the combination of references fairly suggested to one of ordinary skill in the art at the time of the invention how to make hG-CSF lacking an N-terminal methionine.

Applicant further urges that the instant claims are distinguished over Kuga because they are directed to a non-glycosylated hG-CSF, unlike the hG-CSF of Kuga et al. This has been fully considered but is not found to be persuasive. After careful consideration of the evidence of record and the relevant art, it has been determined that the *E. coli*-produced hG-CSF of Kuga also was not glycosylated as an inherent property of that molecule, since production of mammalian proteins in *E. coli* results in a non-glycosylated product. As evidence of such, Applicant's attention is directed to DeFrees et al. (2006, Glycobiology 16:833-843) who clearly state that several mammalian glycoproteins "such as granulocyte colony stimulating factor (G-CSF), interferon-alpha2b (IFN-α2b), and granulocyte/macrophage colony stimulating factor (GM-CSF) are naturally *O*-glycosylated human glycoproteins but are manufactured by recombinant expression in *E. coli* as non-glycosylated polypeptides" (p. 833, bottom of right column). The fact that *E. coli*-produced hG-CSF was not glycosylated was also appreciated at the time of the invention by Souza et al. (1986, Science 232:61-65), who explain such at p.

62, top of middle column. Thus, the hG-CSF of Kuga also contained no sugar chain, as specified in the claims.

Claims 9 and 10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kuga et al. in view of EP 0256843A1 as applied to claims 1-8, 18, 19, 21-24, 26, and 27 above, and further in view of Builder et al. (US 5451660).

The teachings of Kuga et al. and EP 0256843A1 are discussed above.

Kuga et al. do not teach use of the *E. coli* thermoresistant enterotoxin II signal peptide. However, this was well known in the art at the time of the invention.

For example, Builder et al. disclose the use of the *E. coli* thermoresistant enterotoxin II signal peptide to recombinantly express a mammalian secreted protein in *E. coli.* See Example I, section B, columns 14-15. Also note suggestion of G-CSF as an appropriate protein for their disclosed method at column 8, line 22.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the G-CSF constructs of Kuga et al. by deleting the N-terminal methionine as suggested by EP 0256843A1 and using the *E. coli* thermoresistant enterotoxin II signal peptide of Builder et al. with a reasonable expectation of success. The motivation to do so can be found in Builder et al. who describe the benefits of using that particular signal sequence.

Thus, the claimed invention as a whole was *prima facie* obvious over the prior art.

In the after final amendment of 14 September 2007, Applicant argues that they are unaware of any external sources or references that would motivate one of ordinary skill in the art to combine the teachings of Kuga et al. with wither EP 0256843A1 o Builder et al., unless impermissible hindsight is used. This has been fully considered but is not found to be persuasive. It is respectfully submitted that one of ordinary skill in this art would have been aware that recombinant production of mammalian proteins in *E. coli* inherently resulted in non-glycosylated proteins as evidenced by Souza et al. and Rinderknecht et al. Further, one of ordinary skill in this art would have been aware that recombinant production of mammalian proteins in *E. coli* using the enterotoxin II signal peptide would have resulted in successful production despite the lack of an N-terminal methionine as evidenced by Builder et al. Therefore, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Claim Objections

Claims 17, 20, and 25 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ECK

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646